REMARKS

Claims 1-23 and 25-27 were pending in this application. Claims 1, 2, 20, 25 and 27 have been amended. Claim 23 is canceled herein. New claim 28 is added herein. Support for new claim 28 can be found throughout the specification, such as, but not limited to, page 44. Applicants expressly reserve the right to pursue any canceled subject matter in a continuation application.

Applicants believe no new matter is introduced by the foregoing amendments. After entry of this amendment, **claims 1-22 and 25-29 are pending in this application.** Reconsideration of the pending claims is requested.

Rejections Under 35 U.S.C. § 112, first paragraph

Claim 20 is rejected under 35 U.S.C. § 112, first paragraph, as allegedly there is insufficient antecedent basis for the limitation "anti-retroviral drug." Applicants believe there is a typographical error in the Office action, and that the rejection is actually asserted under 35 U.S.C. § 112, second paragraph. Claim 20 is amended herein to depend from claim 19, thereby rendering the rejection moot.

Rejections Under 35 U.S.C. § 102

Claims 1-3, 7-8, 14-17, 21, 23, and 25-27 are rejected under 35 U.S.C. 102(e) as allegedly being anticipated by U.S. Patent Application No. 10/502,085 (hereinafter as "Jiang"). Claim 23 is canceled herein. Applicants respectfully disagree with this rejection as applied to claims 1-3, 7-8, 14-17, 21 and 25-27 as amended.

However, solely to advance prosecution, submitted herewith is a Declaration Under 37 C.F.R. § 1.131 documenting that the inventors conceived and reduced their invention to practice in the United States of America, a WTO country, prior to the effective date (February 4, 2002) of Jiang et al. Thus Jiang is not available as prior art; the submission of the Declaration renders the rejection moot.

Claims 1-3, 7-8, 14-17, 21, 23, and 25-27 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent Application No. 09/874,991 (hereinafter "Mond"). Claim 23 is canceled herein. Applicants respectfully disagree with this rejection as applied to claims 1-3, 7-8, 14-17, 21 and 25-27 as amended.

Mond describes DNA/RNA hybrids that include a CpG motif. These DNA/RNA hybrids are of use as adjuvants. Mond describes that these DNA/RNA hybrids are of use without antigen to stimulate a primary or secondary immune response to an antigen challenge such as for a tumor or to treat "primary challenge by antigenic viruses" (see paragraph 0060). Mond also teaches that the DNA/RNA hybrids are of use for immunosuppression, such as to treat allergy or an autoimmune response (see paragraph 0062), and that these hybrids are of use to globally stimulate the immune system (see paragraph 0078).

However, with regard to the treatment of an HIV infection, Mond teaches the inclusion of the DNA/RNA hybrids in a vaccine (see paragraph 0063 to paragraph 0080). Mond discloses that DNA/RNA hybrids including a CpG motif are of use as adjuvants for vaccines, such as for HIV (see paragraph 0071), Mond describes the use of proteins and haptens from HIV (see paragraph 0076) to produce an immune response to HIV itself. However, Mond does not describe specifically selecting an immunocompromised subject (claims 1 and 25), nor that administration of D type CpG oligodeoxynucleotides (ODNs) (as compared to K ODNs or any other immunostimulatory motif) will boost an immune response without the administration of antigen (claim 25) to a secondary opportunistic infection (claims 1 and 25). Moreover Mond also does not disclose assaying an immune response to the secondary opportunistic infection (claim 1). Thus, Mond does not anticipate claims 1 and 25 as amended, or claims that depend therefrom.

The ability of D ODNs to produce an immune response in an immunocompromised subject to a secondary infection could not be predicted by Mond. Retroviral infection with HIV is associated with a progressive loss of immune function and susceptibility to opportunistic infections. As described in Verthelyi et al. (J. Immunol. 170: 4717-4723, 2003, copy attached as Exhibit A), PBMCs from HIV infected and healthy subjects respond similarly to K-type ODNs (see Fig. 1 of Verthelyi et al.).

However, with regard to D ODNs, the interferon (IFN)-α and IFN-γ response of healthy controls significantly exceeded that of HIV-infected subjects. As shown in Exhibit A, the

reduced responsiveness of D ODNs correlated directly with the number of CD4+ T cells in HIV-infected subjects ($P < 0.01$, see Fig. 3 of Exhibit A and Fig. 3 of the present application). Thus, the response to D ODNs is significantly decreased in HIV-infected subjects. As shown in Exhibit A, PBMCs from simian immunodeficiency virus (SIV) infected macaques responded to K ODNs but had significantly reduced IFN production in response to D ODNs *in vitro*.

As D ODNs were not efficacious in inducing IFN production in immunocompromised subjects, one of skill in the art would not select an immunocompromised subject, such as an HIV or an SIV infected subject for the administration of D ODNs. Based on the teachings of Mond, one of skill in the art would administer K ODNs (as these ODNs stimulate PBMCs from HIV-infected subjects as well as healthy subjects) to induce an immune response to the primary infection namely HIV. Indeed, the superior effect achieved with D ODNs (to produce an immune response in immunocompromised subjects to a secondary opportunistic infection in the absence of treatment with an antigen) could not be predicted based on the teachings of Mond.

Applicants respectfully request reconsideration and withdrawal of the rejection.

Claims 1, 7-17, 21, 23, and 25-27 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,977,245 (hereinafter "Klinman"). Claim 23 is canceled herein. Applicants respectfully disagree with this rejection as applied to claims 1, 7-17, 21 and 25-27 as amended.

Klinman discloses the use of D ODN. Klinman disclose that D ODNs are of use to treat an infection with an infectious agent, such as viruses, see column 18, lines 21-35. Klinman discloses that D ODNs can induce the production of IFN-γ by PBMC (see the Table in column 32). Klinman describes that primates are an effective model to evaluate D ODN (see columns 39-41), and that D ODNs are useful adjuvants in vaccines (see columns 41-42).

However, Klinman does not describe the treatment (or selection of) immunocompromised subjects (claims 1 and 25), nor does Klinman describe opportunistic infections in these immunocompromised subjects, let alone evaluating the immune response to the secondary opportunistic infections (claim1). Furthermore, Klinman et al. do not describe increasing an immune response to a secondary opportunistic infectin in an immunocompromised subject in the absence of an antigen (claims 1 and 25). Thus, Klinman et al. does not anticipate claims 1 or 25, or any claim that depends therefrom.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejections Under 35 U.S.C. § 103(a)

Claims 1-6 and 18-20 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Jiang, Horner et al. (2001) and Fraternale et al (2000).

As discussed above, Jiang et al. is not available as prior art.

Horner et al. describe the use of immunostimulatory DNA sequences (ISS) from bacterial DNA to promote an immune response against HIV. Horner et al. define these ISS as including the motif 5'-purine-purine-CpG-pyrimidine-pyrimidine-3'. Thus, an ISS is not a D ODN. Thus, Horner et al. cannot be construed to suggest, nor render obvious the use of completely differently oligonucleotides, namely D ODN.

Moreover, Horner et al. describe that an ISS in combination with, or conjugated to, gp120, can be used to produce an immune response to activate the immune system and produce a gp120-specific immune response (see Fig. 3), and thus can be used to treat an HIV infection. Thus, Horner et al. conclude that ISS can be used in conjunction with very specific antigens to produce immune response to these antigens themselves. Horner et al. do not describe the production of an immune response to a secondary opportunistic infection, nor do they describe measuring any immune response to any pathogen other than HIV. Indeed, Horner et al. conclude that an "ISS-based vaccine, such as the gp120:ISS conjugate, elicit a multifaceted immune response with characteristics thought to be important for protection against HIV..." (see page 1590). Thus, Horner et al. only describe the production of an antigen specific immune response to a primary infectious agent (HIV).

Fraternale et al. describe the inhibition of murine AIDS by administering aziodthymidine and fludarabine monophosphate in combination therapies. Fraternale et al. do not describe the use of any ODNs, let alone D ODNs. The effects on the blood lymphocytes and spleen are described. Fraternale et al. do not describe the effect of aziodthymidine and fludarabine monophosphate, or any other agents on an immune response to a secondary opportunistic infection.

Even if one of skill in the art were to combine the teachings of Horner et al. with Fraternale et al., one of skill in the art would use an ISS-antigen conjugate with pharmaceutical

antiretroviral agents such as aziodthymidine and fludarabine monophosphate. Thus, the claims clearly are novel and non-obvious over Horner et al. in combination with Fraternale et al.

As discussed above, with regard to D ODNs, the interferon (IFN)-α and IFN-γ response of healthy controls significantly exceeded that of HIV-infected subjects. The reduced responsiveness of D ODNs correlated directly with the number of CD4+ T cells in HIV-infected subjects ($P < 0.01$, see Fig. 3). Thus, the response to D ODNs is significantly decreased in HIV-infected subjects. PBMCs from simian immunodeficiency (SIV) infected macaques responded to K ODNs in vitro, but had significantly reduced IFN production in response to D ODNS. As D ODNs were not efficacious in inducing IFN production in immunocompromised subjects (see Fig. 3 of the present application), one of skill in the art would not select an immunocompromised subject, such as an HIV or an SIV infected subject for the administration of D ODNs. Furthermore, even if one were to administer a D ODN to an immunocompromised subject, one of skill in the art would predict that a sub-optimal immune response to HIV would be generated, in view of the decreased IFN production induced by D ODNs in these subjects. Thus, one of skill in the art would not be motivated to use D ODNs to treat HIV, let alone to treat a secondary opportunistic infection in these subjects. Thus, the effects documented in the present application with regard to the use of D ODNs to produce an immune response to a secondary opportunistic infection were unpredictable.

Results are presented in the specification documenting that D ODNs produce an unexpectedly superior effect at inducing an immune response to secondary infections with Leishmania (see Example 5) and Listeria (see Example 6) in immunocompromised subjects. The efficacy of D ODN to induce an immune response to a secondary opportunistic infection in the absence of treatment with an antigen is demonstrated (see Examples 5 and 6).

Applciants submit that the claimed methods are clearly non-obvious over any of the prior art of record. Applicants respectfully request reconsideration and withdrawal of the rejection.

Conclusion

It is believed that a brief discussion of the merits of the present application may expedite prosecution. This request is being submitted under MPEP §713.01, which indicates that an interview may be arranged in advance by a written request.

Respectfully submitted,

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